

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of

OSBORNE et al.

Atty. Ref.: 620-412; Confirmation No. 4519

Appl. No. 10/567,453

TC/A.U. 1633

Filed: February 7, 2006

Examiner: Marvich

For: MYELOMA CELL CULTURE IN TRANSFERRIN-FREE LOW IRON MEDIUM

\* \* \* \* \*

October 30, 2011

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**SUPPLEMENTAL RESPONSE**

Supplemental to the request in the Request for Continued Examination of September 2, 2011, that the Examiner consider the Response After Final Rejection and Field Declaration filed July 6, 2011, entry and consideration of the following remarks are also requested.

The following remarks were submitted as a part of the REQUEST FOR NEW ACTION AND CONSIDDERATION OF EVIDENCE OF RECORD filed October 13, 2011, that was treated as a Petition Under 37 CFR § 1.181, in the Petition Decision of October 26, 2011, however the applicants wish to ensure consideration of the following by the Examiner with the previously submitted remarks and evidence of record prior to the Examiner's issuance of a new Office Action consistent with the Petition Decision.

The applicants note that the Examiner's comments in the Office Action of October 5, 2011 appear to rely on assertions similar to those raised in the Advisory Action of July 22, 2011 wherein the Examiner asserted that "Fields et al [U.S. Patent No. 6,593,140<sup>1</sup>] teaches the FAC can serve as an iron chelator in growth of myeloma cells." See also page 7 of the Office Action dated October 5, 2011 ("Specifically, Fields et al teach the use of FAC as an iron chelator for growth of cells including myeloma cells..... Fields et al teaches use of FAC in growth methods.").

The evidence presented in the Field Declaration discusses the disclosure of the cited art and explains that while Figure 2A of the cited Field patent shows that high concentrations of iron in the culture medium are required in order to transport iron into hybridoma cells in culture in static flasks in the absence of either transferring or lipophilic iron chelator (e.g. tropolone), in cultures of hybridoma cells that are shaken or agitated (to simulate a fermenter/bioreactor environment) it was shown by Field that for some hybridomas, high iron concentrations in the absence of transferring or a chelator resulted in cell death. Field states that Figure 2B of his patent demonstrates this resulting cell death. Field explains in the Declaration filed July 6, 2011 that these results were the basis for the use by the Field patent of tropolone to supply iron to the hybridoma and other cells in culture by only using a low iron concentration.

Field goes on to explain in the Declaration filed July 6, 2011 that it was surprising and unexpected that although hybridoma cells – which are a fusion of a myeloma cell and a B lymphocyte – are destroyed by higher levels of iron supplied as

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<sup>1</sup> The inventor of U.S. Patent No. 6,593,140 is Raymond Paul Field, who is also the Declarant of

Ferric Ammonium Citrate (FAC) in agitated suspension culture in the absence of transferring or a chelator (as taught by Field), myeloma cells – which are one fusion partner of a hybridoma – can thrive and grow with the same iron levels under similar conditions, as demonstrated in the present application. Field explains, for example, that this was surprising since hybridoma cells and myeloma cells in all other aspects of culture process parameters behave essentially identically to each other; and often differently to many other cell types, such as CHO cells.

In the Advisory Action of July 22, 2011, the Examiner asserts that the basis for the rejection is that Gorfien teaches the instant method, but does not provide details of the iron chelator. The Examiner turns to Field, where allegedly FAC is taught as an iron chelator for growth of myeloma cells. This is factually incorrect as Field emphatically does not illustrate *growth* of myeloma cells. Field very clearly teaches away from the use of FAC for *growth* of cells as evidenced by Example 5 of Field “myeloma cells failed to thrive and died within 48 hours”. Failure to thrive is clearly the opposite of *growth*.

Contrary to the Examiner’s statement that “One would looking at the methods of Gorfien et al be motivated to sue FAC as Gorfien et al directs one to ferric citrate chelators in the methods of growing myeloma cells “ [sic], a skilled artisan would not contemplate using FAC as described in Field in the method of Gorfien because Field clearly shows in Example 5 that myeloma cells grown using FAC did not grow.

The Examiner states that “The failures of Fields et al are not demonstrated to be due to use of FAC but most presumably by differences in the methods of Fields et al

and Gorfien et al.” It is not apparent how the Examiner arrives at this conclusion. Field et al demonstrate that myeloma cells do not grow in the presence of FAC and the absence of transferrin. This demonstration is in agreement with the whole body of art available at the time, as discussed in previous responses. Gorfien does not provide any results at all on the ability of myeloma cells to grow when ferric citrates replace transferrin. The Examiner is incorrect to say that Fields’ failure and Gorfien’s success is due to different methods when Gorfien does not demonstrate successful growth but Field does demonstrate failure to grow.

Furthermore, Figure 2b of Field shows no growth of hybridoma cells in shaking T-flask cultures where FAC is used as the iron source in the absence of transferrin. This example demonstrates that the higher the concentration of FAC used, the less number of cells are viable. This is a clear teaching away from the use of FAC and cannot be dismissed based on the Examiner’s assertion that the failure of growth in Field is due to the difference in the methods of Gorfien and Field. If the skilled person took the teaching of Field into account, he would be taught that FAC does not support growth of myeloma or hybridoma cells in the absence of transferrin, and that increasing the concentration of FAC reduces the viability of hybridoma cells even further (no equivalent data is shown or discussed for myeloma cells). The person skilled in the art would have to go against that teaching and attempt to use FAC in combination with the methods of Gorfien. This clearly demonstrates inventive activity on behalf of the inventors.

The cited combination of art provides no reasonable expectation that the presently claimed method would be achievable. The results of Field would deter the

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skilled artisan from using FAC when attempting to grow myeloma cells in the absence of transferrin.

Consideration of the entirety of the previously filed evidence, and a new Action or Notice of Allowance are requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required to place the application in condition for allowance.

Respectfully submitted,

**NIXON & VANDERHYE P.C.**

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